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DEPARTMENT OF HEALTH & HUMAN SERVICES

New York District

Food & Drug Administration
158-15 Liberty Avenue
Jamaica, NY 11433

March 14, 2003

WARNING LETTER

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Ref: NYK-2003-15

Mr. Muhammed Malik
President
Syntho Pharmaceuticals, Inc.
230 Sherwood Avenue
Farmingdale, NY 11746

Dear Mr. Malik:

During an inspection of your drug manufacturing facility located in Farmingdale, New York, conducted on October 21-24, 28, 30-31, 2002 and November 4-7 & 20, 2002, our investigators documented deviations from the Current Good Manufacturing Practice (CGMP) for Finished Pharmaceuticals Regulations (Title 21, Code of Federal Regulations (CFR), Parts 210 and 211). Such deviations cause your drug product, Syntest tablets (Esterified Estrogens and Methyltestosterone), to be adulterated within the meaning of Section 501(a)(2)(B) of the Federal Food, Drug and Cosmetic Act (the Act) (21 U.S.C. § 351(a)(2)(B)) as follows:

1. Failure to validate the performance of those manufacturing processes that may be responsible for causing variability in the characteristics of in-process materials and drug products as required by 21 CFR 211.110, in that validation studies have not been performed for Syntest manufacturing processes including blending, tableting, coating, and packaging. Although your firm has a validation protocol requiring that the first three commercial batches of Syntest be validated, there is no record of such validation ever having been performed.

2. Laboratory controls fail to include the establishment of written, scientifically sound specifications, standards, sampling plans, and test procedures designed to assure that components, drug product containers, closures, in-process materials, labeling and drug products conform to appropriate standards of identity, strength, quality, and purity as required by 21 CFR 211.160(a) and (b) in that:

(a) Your firm lacks a complete written method that fully describes the procedure, equipment, parameters, and specifications to be used in the analysis of Syntest tablets.

(b) There are no written procedures to address out of specification results.

(c) Further, your written procedures do not address laboratory records in that there are no written procedures directing the review of analytical testing performed by a second person to assure accuracy, completeness, and compliance with established standards and the documentation of such a review with the individuals initials or signature as required by 21 CFR 211.194(a)(8).

3. The accuracy, sensitivity, specificity, and reproducibility of test methods employed by your firm are not established and documented as required by 21 CFR 211.165(e) in that there is no validation data for the method used to analyze Syntest tablets.

4. Failure to follow your firm's written stability testing program as required by 21 CFR 211.166(a) in that your firm has no validation data to demonstrate that the method used to analyze Syntest Tablets for stability is capable of detecting degradation.

   Further, your firm failed to test an adequate number of batches of Syntest tablets to determine a tentative expiration date in accordance with 21 CFR 211.166(b). For example: Accelerated stability studies were begun in April 2002 for Lots S02D01 and S02D02 and were not complete until 7/22/02, yet these lots were shipped to a customer on 4/30/02.

5. Your firm does not have an SOP describing calibration procedures to be used for your firm's liquid chromatographs. Further, there are no records of chromatograph calibration performed as required by 21 CFR 211.160(b)(4) and 211.194(d).

   Calibration deficiencies were noted with other equipment as well. The balances were observed to have tags affixed bearing calibration dates of May 2002, with scheduled recalibration due on July 2002. But the balances had not been calibrated as of the close of the inspection.

6. Failure to verify the suitability of all testing methods under actual conditions of use as required by 21 CFR 211.194(a)(2). For example: With respect to the chromatographic system used for Syntest, only three standards are injected at the beginning of the analyses. No RSD is calculated to ensure reproducibility of the chromatographic system and no other system suitability tests are recorded in the notebook or on the chromatograms.

7. Failure to conduct a thorough investigation of unexplained discrepancies or the failure of a batch or any of its components to meet any of its specifications as required by 21 CFR 211.192. For example:

   (a) For the uniformity of dosage unit analysis of Syntest tablets, lot S02K03, three of the first ten tablets tested were outside the USP limit of 85-115% for methyltestosterone. An additional twenty tablets were tested and averaged with the original ten; the average was then reported as a passing result. The lot was released and a certificate of analysis claimed that the product meets USP requirements for uniformity of dosage units even though the USP specification states that no more than one tablet can be outside the 85-115% limit.

   (b) For the assay analysis of Syntest Tablets, lot S02J04, your firm obtained out of specification results of 89.42% and 89.73% for methyltestosterone. The limit is 90-110%. A third assay was performed and the result was 90.92% Your firm combined the three results, obtained an average of 90.03%, and reported the results as meeting requirements without any further investigation of the failing test results.

   (c) For the assay analysis of Syntest tablets, lot S02K02, your firm obtained one out of specification result of 88.15% and one passing result of 95.72% for methyltestosterone. These two results were averaged to a result of 91.93% and reported as meeting requirements without any further investigation of the failing test result.

8. Failure to adequately clean and maintain equipment at appropriate intervals to prevent malfunctions or contamination as required by 21 CFR 211.67(a). Our inspection found that your firm reuses isopropyl alcohol several times before discarding it. This practice is utilized for Syntho equipment as well as other facility equipment processing a variety of drug products. Cleaning procedures have not been validated to assure the adequacy of this cleaning procedure in preventing contamination.

9. Failure to document the review and approval of changes to written procedures for production, process, and laboratory controls by the appropriate organizational unit and quality control as required by 21 CFR 211.100(a) and 21 CFR 211.160(a), i.e., changes made to SOPs regarding cleaning validation, stability sampling, and in-process control.

10. Failure to provide employee training on a continuing basis to assure their knowledge and understanding of the drug CGMP regulations as they relate to their assigned functions as required by 21 CFR 211.25. Although your firm has a written procedure for training, it was found that these procedures are not followed. For example, the procedures require training to be conducted six times annually, but only one record of GMP training

was available dated August 5, 2002. The procedures also require documentation by supervisors of CGMP training for all new employees as they relate to each department, but no such documentation was available.

11. Failure to identify each lot as to its status (i.e., quarantined, approved, or rejected) as required by 21 CFR 211.80(d) in that the only designation made for raw materials is for approved components. This designation is made verbally from the Quality Control lab to Quality Assurance who applies "approved" labels to each container.

12. Failure to limit access to the label storage area to authorized personnel in accordance with 21 CFR 211.122(d) in that the room was observed to be unlocked with access by all personnel. Various individuals were observed entering the room throughout the inspection.

13. Failure to document each significant step in the manufacture, processing, packing, or holding of a batch in batch production and control records as required by 21 CFR 211.188(b) in that:

    (a) Results of examinations of drug product inspections were not recorded as required by 21 CFR 211.188(b)(13). Investigators found employees repackaging approximately 230 bottles of Syntest lot S02K04 because labels had not been applied properly, yet the batch record made no reference to this reprocessing operation.

    (b) Batch records fail to identify individual pieces of major equipment used as required by 21 CFR 211.188(b)(2) since there is no designation identifying multiple units of the same equipment.

    (c) Laboratory control results are not included in batch records as required by 21 CFR 211.188(b)(5). Analytical results are only maintained in laboratory notebooks.

14. Failure to establish written procedures for use of suitable rodenticides, insecticides, fungicides, fumigating agents, and cleaning and sanitizing agents as required by 21 CFR 211.56(c).

We acknowledge receipt of your letter dated December 17, 2002 relaying your firm's intended corrective actions relating to the Inspectional Observations issued to you on November 20, 2002. However, your letter is of a general nature and does not address any specific corrective actions to the multiple violations cited. There is no accompanying documentation addressing any corrective action or time frames specified for correction. Your letter indicates that you strongly disagree with some of the observations made by the investigators, but your response provides no insight as to basis for this statement. In addition, we note that your letter states Syntho has shipped only [redacted] batches of Syntest for distribution, yet shipping records obtained during the inspection revealed [redacted] shipments: [redacted]

[redacted]. In light of the above, your response is not adequate in addressing the violations cited on the form FDA 483.

Neither the identification of violations in this letter nor the inspectional observations (Form FDA 483)(copy enclosed) presented to you at the conclusion of the inspection is intended to be an all-inclusive list of deficiencies at your facility. It is your responsibility to ensure adherence with each requirement of the Act and its implementing regulations. Federal agencies are advised of the issuance of all warning letters about drug products so that they may take this information into account when considering the award of contracts.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action with further notice. These include seizure and/or injunction.

You should notify this office upon receipt of this letter to arrange for a meeting to discuss the specific steps you have taken to correct the noted violations, including an explanation of each step being taken to prevent the recurrence of similar violations. If corrective action cannot be completed within 15 working days, state the reason for delay and the time within which corrections will be completed.

Your reply should be sent to Compliance Branch, Food and Drug Administration, 158-15 Liberty Avenue, Jamaica, NY 11433. Attention: Lillian C. Aveta, Compliance Officer.

Sincerely,

Jerome G. Woyshner
District Director
New York District

Enclosure: Form FDA 483 dated November 20, 2002